REMARKS

Upon entry of the forgoing amendments claims 1-17 are pending in the instant application. Claims 18 and 19 have been amended without prejudice or disclaimer to the subject matter contained therein. Claims 1 and 17 have been amended to clarify the subject matter contained therein. The amendments do not introduce any new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendments is respectfully requested.

OBJECTION TO THE SPECIFICATION

The disclosure has been objected to based on the following informalities: the brief description of the drawings section is not identified by a title and the description does not describe the variables in each respective figure legend and the abstract contains the term "said".

Applicants respectfully submit that the specification has been amended in order to correct the points above-identified by the Examiner. Specifically, a title has been added to identify the "Brief Description of the Drawings" section and the descriptions of the relevant figures have been amended to describe the variables contained in the respective figure. The Abstract has further been amended to remove the term "said".

Accordingly, all bases for these objections have been removed, and therefore the Examiner is respectfully requested to reconsider and withdraw the objections.

REJECTION UNDER 35 U.S.C. §101

The Examiner has rejected claims 18 and 19 as being directed to a method of use without setting forth any steps involved in the process.

Applicants respectfully submit that claims 18 and 19 have been cancelled without prejudice or disclaimer to the subject matter contained therein.

Accordingly, the basis for this rejection has been removed, and therefore the Examiner is respectfully requested to reconsider and withdraw this rejection.

REJECTIONS UNDER 35 U.S.C. §112

The Examiner has rejected claims 1 and 17-19 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, the Examiner has stated that in claim 1 there is no antecedent basis for the phrase "the fusion polypeptides", that in claim 17 there is no antecedent basis for the phrase "the modified nucleic acid" and that claims 18 and 19 provide for various methods without setting forth and steps involved in the method.

Applicants respectfully submit that in claim 1 the term "the" has been deleted from the phrase "the fusion polypeptides" thereby rectifying the lack of antecedent basis noted by the Examiner. Likewise in claim 17, the lack of antecedent basis for the phrase "the modified nucleic acid" has been overcome by amendment, wherein the dependency of claim 17 has been changed to claim 10, which does recite "modified nucleic acid". Finally, as noted above, claims 18 and 19 have been cancelled without prejudice or disclaimer to the subject matter contained therein.

Accordingly, all bases for these rejections under 35 U.S.C. §112 have been removed, and the Examiner is respectfully requested to reconsider and withdraw these rejections.

REJECTIONS UNDER 35 U.S.C. §103

The Examiner has rejected claims 1-17 under 35 U.S.C. §103(a) as being unpatentable over Epstein et al. ("Epstein"), in U.S. Patent No. 5,856,090, in view of Doi and Yanagawa ("Doi"), in FEBS Lett 457(2): 227-230 (1999).

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Furthermore, there must be something in the prior art that provided reason to make the combination of the references other than the hindsight gained from knowing that the inventor chose to combine the particular things in this particular way. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988). The mere presence of an element of the claims in a reference without a reason to combine and some indication of a likelihood of success is not sufficient to maintain a *prima facie* case of obviousness. The mere fact that references can be combined or modified does not render the combination obvious unless the reference suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990).

Epstein teaches a method for covalently coupling genotype (DNA) to phenotype (protein) using a DNA methyltransferase-polypeptide fusion protein *in vitro*. Specifically, Epstein disclose special strains of *E. coli* transformed with a plasmid containing the gene for a DNA methyltransferase-polypeptide and several methylation target sequences (about 3-20) are grown in liquid medium. After production of the DNA methyltransferase-polypeptide fusion proteins, cytidine analogs are added to the bacterial culture (preferably 2'-deoxy-5-azacytidine or 2'-deoxy-5-fluorocytidine). During DNA synthesis within the bacteria, the cytidine analogs are randomly integrated in the newly formed DNA (that is both bacterial genomic DNA and plasmid DNA). As a result of the incorporation of the cytidine analogs into methylation target sites instead of the standard base cytidine, DNA methyltransferases become covalently cross-linked with DNA at theses target sites. Covalent DNA-protein fusions are then extracted from the bacteria and are used for the selection of binding proteins. Epstein suggests many different DNA methyltransferases could be used with his methodology. The preferred enzymes encompass the methylases MspI, AquI, and HhaI.

Applicants respectfully submit that statistically a defined DNA sequence of four bases (e.g. CCGG) has frequency of 1:256 and defined DNA sequence of six bases of 1:4096. Since the genome of commonly used K-12 derived *E. coli* laboratory strains contains 4.6 million bases, there are 17,960 CCGG recognition sites for MspI methylase and 2,240 CCCGGG or CTCGAG recognition sites for AquI methylase within the genomic DNA for bacteria. It is obvious to a person of skill in the art that methylase fusion proteins expressed in these bacteria will not only covalently bind to the plasmid but also to a large extent to genomic DNA. The DNA fragments not coding for the attached protein will result in the recovery of many false positive DNA fragments in the subsequent affinity selection procedure.

Furthermore, Applicants respectfully submit that the method disclosed by Epstein further suffers from the disadvantage that the number of methylase fusion proteins that are bound to the plasmid cannot be defined exactly. Polyvalent display can lead to the selection of weak binding proteins due to avidity effects. With monovalent display, however, strong binding candidate

proteins are more efficiently recovered than weak binders which lead to an efficient enrichment of binding proteins.

Esptein proposes PCR to amplify the genes recovered from the affinity selection. However, methylases covalently bound to the DNA to be amplified will hinder successful DNA amplification. Moreover, the size of the polypeptide library is limited due to the *in vitro* binding of genotype to phenotype.

In summary, Epstein discloses growing strains of *E. coli* transformed with a plasmid containing gene for a DNA methyltranferase-polypeptide and several methylation target sequences (about 3-30) resulting in methylase fusion proteins expressed in the bacterial that covalently bind to the plasmid but also to a large extent to genomic DNA.

Doi do not remedy the deficiencies of Epstein. Specifically, Doi teaches an *in vitro* selection system for the isolation of binding polypeptides relying on an *in vitro* transcription/translation reaction within the compartments of a water-in-oil emulsion. In each water compartment streptavidin (STA)-fused polypeptides are synthesized and attached to the encoding DNA via its biotin label. The resulting protein-DNA complexes extracted from the emulsion can be subjected to affinity selection based on the properties the peptide portion, whose sequence can be determined from that of the attached DNA molecule.

Doi disclose the very well known and tight streptavidin-biotin interaction to link DNA and protein. However, it is known that expression of streptavidin in *E. coli* leads to insoluble aggregates of non-functional streptavidin molecules within the cells (inclusion bodies). Thus, the efficiency of the system proposed by Doi et al. is limited by the low expression level streptavidin. The same expert group including Nobuhude Doi discloses this in 2003 (See, Yonezawa et al. ("Yonezawa"), attached). Yonezawa teaches that the efficiency of DNA-peptide conjugate formation could be improved by using a wheat germ *in vitro* transcription/translation system. See, Yonezawa, p. 1, col. 2, lines 16-25 and p. 3, col. 2, lines 6-8.

However, Applicants respectfully submit this method still suffers from the fact that only either four or eight copies of the peptide can be displayed per DNA molecule, since streptavidin is a tetrameric protein with four biotin binding sites per tetramer. Therefore, exact control of polyvalent vs. monovalent display is not possible. Moreover, only streptavidin-peptide fusions are disclosed; there is no experimental evidence that folded proteins can be fused to streptavidin and expressed *in vitro*.

Doi provide clear indication that other DNA binding proteins could also be used as adapters for DNA-protein linkage. See, p. 229, paragraph bridging col. 1-2, citing Cull et al. However, the reference Cull et al. again teaches the binding protein and DNA as a non-covalent complex. See Cull et al., abstract and page 1865.

In summary, Doi teach the cis conjugation of streptavidin-polypeptide conjugates transcribed and translated in aqueous compartments in a water-in-oil emulsion and suggest the use of other non-covalent protein-DNA complexes.

The Examiner asserts "it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a nucleic acid polypeptide conjugate using the water-in-oil emulsion microcompartment because Doi and Yanegawa disclose the *in vitro* transcription-translation in a water-in-oil emulsion and subsequent nucleic acid polypeptide conjugation." Supposedly, an additional motivation for using microcompartments would have been the desire to prevent contaminants from degrading the nucleic acid and amino acid molecules.

However, Applicants submit that there is no record in the prior art that would generally provide reason to the skilled person to deviate from cells towards microcompartments because this is a highly specific and not general issue, which depends on the specific polypeptide and nucleic acid sequence. Microcompartments were not an issue in Epstein, nor did they become so later on, and therefore, there is no factual basis in the reference for this assertion.

Likewise, Applicants respectfully submit that the extension of the Examiner's line of reasoning is that one of skill in the art would employ the water-in-oil emulsion microcompartments of Doi simply because it could be done is supported by no factual or scientific basis. One of skill in the art would not seek any deviation from the *E. coli* cells of Epstein, because said cells are convenient due to their ability to carry the translation and transcription machinery and propagation of the cells is simple and cost efficient.

Furthermore, Doi do not deviate from their concept of non-covalent peptide-nucleic acid conjugates. Instead, Doi specifically recommended other non-covalent systems, such as that of Cull et al., and make subsequent efforts to improve the streptavidin-biotin system.

Hence, there is absolutely no reason in either of the cited references or in the knowledge generally available to one of ordinary skill in the art to modify or combine the teachings of Epstein and Doi to arrive at the instant subject matter. On this basis, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection.

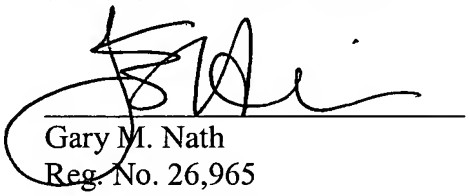
CONCLUSION

Based upon the foregoing, Applicants respectfully request the Examiner to reconsider and withdraw the outstanding objection and rejections to the claims and allow all pending claims in the application.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to contact the undersigned attorney.

Respectfully submitted,

THE NATH LAW GROUP



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